REMARKS

Claims 1-72 are active in the present application. Claims 1-45 and new Claims 46-72 are drawn to the elected invention. Favorable reconsideration is respectfully requested.

The present invention provides nucleic acid probes that solve the long-standing problem of those probes known previously (see page 4, lines 15-24 of the present specification) by enabling the determination of "the concentration of target nucleic acids in shorter times, more easily and more accurately" (page 2 , first paragraph of the present specification). The inventors have "found that emission of fluorescence from a fluorescent dye decreases (quenching phenomenon of fluorescence) when a nucleic acid probe labeled with the fluorescent dye hybridizes to a target nucleic acid. . . [the inventors have] also found that the extent of this decrease varies depending on bases in a probe portion, to which the fluorescent dyes is conjugated, or on the sequence of bases" (page 2, line 18 to page 3, line 1 of the present specification). Based on this discovery the present invention provides probes as claimed in Claims 2, 5, 48 , 61 and dependent claims thereon. The invention also provides kits and devices incorporating these probes and methods of determining the concentration of a nucleic acid.

The advantages of the present invention are shown in the Examples section of the present application found on pages 65-108. In addition, Applicants provide data in the form of an executed Declaration under 37 C.F.R. § 1.132 that demonstrates consistent quenching rates with BODIPY FL fluorescent dye (see Claims 47, 60, and 73) when used in a hybridization experiment.

The objection to Claims 9-11, 15, 21 and 23-26 is obviated by amendment. The claims have been amended to remove multiple dependencies.

The rejection of Claim 8 under 35 U.S.C. § 112, second paragraph is obviated by amendment. The spelling of "phosphorylated" has been corrected.

The rejection of Claims 2-6 under 35 U.S.C. § 102(b) over Squirrell et al (U.S. Patent No. 5,750,337) is respectfully traversed.

Squirrell et al disclose a nucleic acid molecule that has a G or C at the ends of the molecule and which is labeled with a fluorescent dye (see col. 6, Table 1: "SEQ ID NO:2"). However, Squirrell et al do not disclose a probe that is designed such that when it hybridizes to the target nucleic acid, at least one G (guanine) exists in the base sequence of **the target nucleic acid** 1 to 3 bases from the end of the probe-target binding site (see Claim 2). Accordingly, Claims 2-6 are not anticipated by Squirrell et al and as such withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 5, 7 and 8 under 35 U.S.C. § 102(b) over Tsang et al (U.S. Patent No. 5,837,442) is respectfully traversed.

Tsang et al disclose a probe "KY150" corresponding to SEQ ID NO:43 from US Patent 5,527,669 having the sequence: 5'-CATAGTGGTCTGCGGAACCGGTGAGT-3'. As stated in Tsang et al: "The probe was synthesized with fluroescein . . . bound at the 5' end and a 3'PO_4 instead of 3'-OH to block any extension by the DNA polymerase" (col. 9, lines 3-7). However, Tsang et al do not disclose a probe as claimed in Claim 5: ". . . wherein said probe can be further extended at it's 3'-end by a DNA polymerase."

Tsang et al also do not disclose a probe as claimed in Claim 47, which "has a G or C as a 3' end base and is labeled at said 3' end thereof with said fluorescent dye." Again pointing out that Tsang et al disclose a 3'PO_4. Likewise, Tsang et al do not disclose a probe

as Claimed in Claim 60, which has a C as a 5' end base, is labeled at the 5' end with a fluorescent dye **and** where a hydroxyl group of a 2' or 3' carbon of a ribose, or a 3' carbon of a deoxyribose at the 3' end of the probe is phosphorylated. Because Tsang et al do not disclose the instant invention, the rejection over Tsang et al is unsustainable. Accordingly, withdrawal of this ground of rejection is respectfully requested.

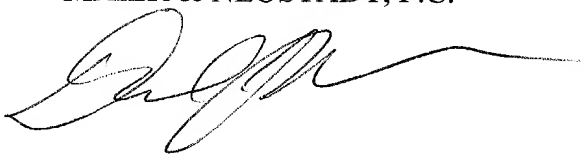
The references listed in the attached Information Disclosure Statement were cited in the co-pending Divisional Application of the present application: U.S. Serial No. 09/725,265 filed November 29, 2000.

Applicants submit that the present application is now in a condition for allowance.

Early notice of such allowance is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

Daniel J. Pereira, Ph.D.
Registration No. 45,518

22850

(703) 413-3000
Fax #: (703) 413-2220
NFO/DJP

H:\01630758-am.wpd

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IN THE CLAIMS

Please amend the claims as follows:

3. (Amended) [A] The nucleic acid probe according to claim 2, wherein said probe is labeled at a 3' end thereof with said fluorescent dye.

4. (Amended) [A] The nucleic acid probe according to claim 2, wherein said probe is labeled at a 5' end thereof with said fluorescent dye.

5. (Amended) A nucleic acid probe for determining a concentration of a target nucleic acid, said probe being labeled with a fluorescent dye, wherein:

said probe is labeled at an end portion thereof with said fluorescent dye, and

said probe has a base sequence designed such that, when said probe is hybridized with said target nucleic acid, base pairs in a probe-nucleic acid hybrid complex form at least one G (guanine) and C (cytosine) pair at said end portion;

whereby said fluorescent dye is reduced in fluorescence emission when said probe is hybridized with said target nucleic acid, wherein said probe can be further extended at it's 3'-end by a DNA polymerase.

6. (Amended) [A] The nucleic acid probe according to claim 5, wherein said probe has G or C as a 3' end base and is labeled at said 3' end thereof with said fluorescent dye.

7. (Amended) [A] The nucleic acid probe according to claim 5, wherein said probe has G or C as a 5' end base and is labeled at said 5' end thereof with said fluorescent dye.

8. (Amended) [A] The nucleic acid probe according to claim 4 [or 7], wherein a hydroxyl group of a 2' or 3' carbon of a ribose or a 3' carbon of a deoxyribose at 3' end of said probe has been [phosporylated] phosphorylated.

9. (Amended) [A] The nucleic acid probe according to [any one of claims 1-8] claim 2 or claim 5, wherein an oligoribonucleotide of said probe is a chemically-modified nucleic acid.

10. (Amended) [A] The nucleic acid probe according to [any one of claims 2-8,] claim 2 or claim 5, wherein an oligonucleotide of said probe is a chemiric oligonucleotide comprising a ribonucleotide and a deoxyribonucleotide.

11. (Amended) [A] The nucleic acid probe according to claim 10, wherein said ribonucleotide is a 2'-O-methyloligoribonucleotide.

15. (Amended) A kit for analyzing or determining polymorphism or mutation of a target nucleic acid or gene, comprising a nucleic acid probe according to claim 2 or claim 5 [any one of claims 2-11].

21. (Amended) [A] The kit according to claim 15, further comprising a helper probe for being added to a hybridization reaction system.

23. (Amended) A device for determining concentrations of nucleic acids, comprising:

a solid support, and

a nucleic acid probe according to [any one of claims 2-11] claim 2 or claim 5 or a different nucleic acid probe bound on a surface of said solid support, said different nucleic acid probe having a structure designed such that said probe comprises two fluorescent dyes of different kinds in a molecule and that, owing to interaction between said two fluorescent dyes, said probe quenches or emits fluorescence when said probe is not hybridized with said target nucleic acid but emits fluorescence or quenches when said probe is hybridized with said target nucleic acid;

whereby said device can determine said concentration of said target nucleic acid by hybridizing said target nucleic acid to said probe or said different probe.

24. (Amended) [A] The device according to claim 23, wherein said probes or said different robes are arranged and bound in an array pattern on said surface of said solid support.

25. (Amended) [A] The device according to claim 23 or claim 24, wherein said probes or different probes bound on said surface of said solid support are each independently provided with at least one temperature sensor and at least one heater arranged on an opposite surface of said solid support such that an area of said solid support, where said probe or different probe is bound, can be controlled to meet optimal temperature conditions.

26. (Amended) (Amended) [A] The device according to [any one of claims 23 to 25] claim 23 or claim 24, wherein said probe or different probes are bound at end portions, where

said probes or different probes are labeled with no fluorescent dye on said surface of said solid support.

Claims 46-72 are added.